MedicalXpress

# Discovery of a promising medication for amyotrophic lateral sclerosis

November 16 2017

Researchers from the University of Montréal Hospital Research Centre (CRCHUM) and the Cumming School of Medicine (CSM) at the University of Calgary have discovered a medication that could make it possible to treat individuals with amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease.

An article published today in *JCI Insight* concludes that pimozide was found to be safe and over the short term, preliminary data shows that it could stabilize the progression of ALS. This neurodegenerative disease normally leads to a progressive paralysis of the skeletal muscles and, on average, three years after the onset of symptoms, to death.

"This medication alleviates the symptoms of ALS in animal models," said Alex Parker, a CRCHUM researcher and professor at Université de Montréal. "Riluzole and edaravone, the drugs currently used, have modest effects. Other studies must be conducted to confirm our results, but we believe that we've found a medication that may prove to be more effective in improving patients' quality of life."

## From worm to man

The story behind the discovery began six years ago with a little millimeter-long nematode worm called C. elegans. In his laboratory, Parker genetically modified the worms so that they would exhibit aspects of the human form of ALS. Simultaneously, his colleague Pierre

Drapeau did the same thing to another animal, the zebrafish, a tiny tropical fish only 5 centimetres long.

The two scientists obtained funding from the U.S. Department of Defense to test medications on these worms and fish born with ALS. "We sifted through a library of 3,850 molecules approved for the treatment of other diseases, and found a class of antipsychotic drugs that stabilize mobility in worms and fish," said Drapeau, a CRCHUM researcher, professor at Université de Montréal and principal investigator on the study. "Pimozide works especially well in preventing paralysis in fish by preserving the neuromuscular junction."

Subsequently, Université de Montréal Professor Richard Robitaille performed electrophysiological tests on mice in his laboratory and reached the same conclusion. Thus, pimozide was shown to maintain neuromuscular function in three different animal models: worms, fish and mice.

At the annual ALS Canada Research Forum in 2012, the researchers met Dr. Lawrence Korngut, an Associate Professor at the CSM, member of the Hotchkiss Brain Institute (HBI) and Director of the Calgary ALS/Motor Neuron Disease Clinic. "Pimozide is a drug that has been well-known for 50 years," the neurologist said. "It was approved for treating certain types of psychiatric conditions, like schizophrenia, and costs only 9 cents per pill. Other recent studies have shown genetic links between schizophrenia and ALS. The next logical step was to test it on human volunteers with ALS."

In 2015, the first preclinical trial for ALS was launched in Canada with a small group of 25 patients who had ALS. Funding was provided by the Quirk family of Calgary, by the HBI, and the Clinical Research Unit at UCalgary.

"We found the highest dose most likely to be tolerated in individuals with ALS - a lower dose than that used in other conditions - and we have preliminary proof showing that pimozide may be useful," said Korngut.

The initial clinical trial was modest in scope. But after only six weeks, the researchers had a first indication of the drug's efficacy. Loss of control of the thenar muscles, located in the palm of the hand between thumb and index finger, is usually one of the first signs of ALS. For patients who took pimozide, this function remained stable. This observation is tempered by the very limited size and length of the clinical trial.

"For us, this is an indication that we found the right therapeutic target," said Drapeau. "Pimozide acts directly on the neuromuscular junction, as shown in our animal models. We don't yet know whether pimozide has a curative effect, or whether it only preserves normal neuromuscular function to at least stabilize the disease. This is also the first time that a potential drug for human patients was discovered based on basic research on small organisms such as worms and fish."

Now comes the next step: a phase II clinical trial on 100 volunteers, funded by the "The Ice Bucket Challenge" through a partnership between ALS Canada and Brain Canada to begin in the next few weeks. Headed by Korngut in Calgary and conducted in nine hospital centres across Canada, the study aims to confirm that pimozide is safe and to measure, over a six-month period, its effect on the progression of the disease and its symptoms and on patients' quality of life.

Daniel Rompré, 47, father of two teenage girls, hopes to participate in the new study. He was diagnosed with ALS in March 2016. The muscles of his upper body are getting weaker, he is beginning to have trouble speaking, and he can no longer use his left arm. "It is hard to maintain a positive outlook," Rompré said. "You ask yourself: 'Why me?' But at

least it's encouraging to see that research is advancing. There has been more progress in the last five years than in 100 years of research on the disease."

It is too soon to draw firm conclusions about the safety and efficacy of pimozide. "At this stage, people with ALS should not use this medication," Korngut emphasized. "We must first confirm that it is really useful and safe in the longer term. It is also important to be aware that pimozide is associated with significant side effects. Therefore, it should only be prescribed in the context of a research study."

**More information:** Shunmoogum A. Patten et al, Neuroleptics as therapeutic compounds stabilizing neuromuscular transmission in amyotrophic lateral sclerosis, *JCI Insight* (2017). DOI: 10.1172/jci.insight.97152

Provided by University of Montreal